REMARKS

I. Status Summary

Claims 1-14 and 36-38 are now pending in the subject U.S. patent application as a result of a Restriction/Election Requirement.

The species election requirements related to the metal ion of claim 5 and the chelator donor molecule of claim 11 presented in the Restriction Requirement dated April 19, 2005, have been withdrawn.

Claim 1 has been objected to for the presence of a grammatical error.

Claims 1-3, 5, 8, and 9 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by McMahan *et al.* (236 *Anal Biochem* 101-106, 1996; hereinafter "McMahan"). Claims 1-3, 5, 8, 9, and 36-38 have also been rejected under this section upon the contention that the claims are anticipated by the Product Information for MOLECULAR PROBES™ PRO-Q™ Oligohistidine Blot Stain Kit #2 dated September 27, 2001 (hereinafter the "PRO-Q™ Product Information"). Claims 1, 2, 4, 5, 8, and 9 have also been rejected under this section upon the contention that the claims are anticipated by Ehteshami *et al.* (9 *J Mol Recog* 733-737, 1996; hereinafter "Ehteshami *et al.*"). Claims 1, 2, 4, 5, and 8-14 have also been rejected under this section upon the contention that the claims are anticipated by the 1996 Ph.D. Dissertation of Gholam Ehteshami (hereinafter the "Ehteshami Dissertation").

Claims 1-3, 5-9, and 36-38 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over McMahan or the PRO-Q™ Product Information in view of Neville *et al.* (6 *Prot Sci* 2436-2445, 1997; hereinafter "Neville") and Nieba *et al.* (252 *Anal Biochem* 217-228, 1997; hereinafter "Nieba"). Claims 1, 2, and 4-14 have also been rejected under this section upon the contention that the claims are unpatentable over Ehteshami *et al.* or the Ehteshami Dissertation in view of Neville and Nieba.

Claim 5 has been canceled without prejudice.

Claims 1, 6, 7, and 10 have been amended. Support for the amendment to claims 1 and 10 can be found throughout the specification as filed, including particularly in claim 5 as filed. The amendments to claims 6 and 7 are solely to change the dependency of these claims from claim 5, which was canceled, to the claim from which

claims 6 and 7 originally indirectly depended (*i.e.*, claim 1). Accordingly, applicants respectfully submit that no new matter has been added by the amendments to the claims.

Reconsideration of the application as amended and based on the arguments set forth herein below is respectfully requested.

II. Response to the Objection to Claim 1

Claim 1 has been rejected to on a formal basis. According to the United States Patent and Trademark Office (hereinafter the "Patent Office"), claim 1 recites "an detectable label". Applicants have amended claim 1 to recite "a detectable label", which applicants respectfully submit addresses the instant objection.

III. Responses to the Rejections under 35 U.S.C. § 102(b)

Claims 1-3, 5, 8, and 9 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by McMahan. Claims 1-3, 5, 8, 9, and 36-38 have also been rejected under this section upon the contention that the claims are anticipated by the PRO-Q™ Product Information. Claims 1, 2, 4, 5, 8, and 9 have also been rejected under this section upon the contention that the claims are anticipated by Ehteshami *et al.* Claims 1, 2, 4, 5, and 8-14 have also been rejected under this section upon the contention that the claims are anticipated by the Ehteshami Dissertation. According to the Patent Office, each of these references discloses a chelator-metal moiety wherein the chelator is nitriloacetic acid or iminodiacetic acid and the metal is Ni^{2+} or Cu^{2+}. The references are further asserted to disclose a detectable moiety comprising biotin, the use of a PEG spacer (Ehteshami *et al.* and the Ehteshami Dissertation), a method for synthesizing the conjugate (the Ehteshami Dissertation), and that the conjugate is water soluble.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Initially, applicants respectfully submit that claim 1 has been amended to recite a phosphoprotein detection reagent (PPDR) comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety, wherein (i) the metal ion

is selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}; (ii) the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein if present to create a chelator-metal ion-phosphoprotein (CMPP) complex; and (iii) the detectable moiety allows the CMPP complex to be detected if present. Similarly, claim 10 has been amended to recite a method for synthesizing a phosphoprotein detection reagent (PPDR) that is soluble in an aqueous medium, the method comprising (a) reacting a polydentate chelator donor molecule with a detectable moiety donor under conditions wherein a detectable moiety is transferred to a polydentate chelator to form a chelator-detectable moiety complex; and (b) mixing the chelator-detectable moiety complex and a metal ion-containing solution comprising a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+} under conditions wherein the chelator-detectable moiety complex coordinates the metal ion, forming a PPDR that is soluble in aqueous medium.

As such, applicants respectfully submit that claims 1 and 10 recite that the metal ion that is present in the phosphoprotein detection reagent (PPDR) is Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}. Applicants respectfully submit that the disclosures of the cited references are limited to employing Ni^{2+} or Cu^{2+}, and thus none of these references discloses each and every element of claims 1 and 10.

Accordingly, applicants respectfully submit that the cited McMahan, the PRO-Q™ Product Information, Ehteshami *et al.*, and the Ehteshami Dissertation references do not anticipate claims 1 and 10. Applicants further respectfully submit that claims 2-9 and 36-38 all depend from claim 1, and thus include all the elements of claim 1. Similarly, claims 11-14 depend from claim 10, and thus include all of the elements of claim 10. As such, applicants respectfully submit that claims 2-9, 11-14, and 36-38 are also believed to have been distinguished from the cited references.

Therefore, applicants respectfully submit that claims 1-14 and 36-38 have been distinguished from McMahan, the PRO-Q™ Product Information, Ehteshami *et al.*, and the Ehteshami Dissertation, and respectfully request that the rejections be withdrawn at this time. Claim 5 has been canceled, and thus the rejection as applied to claim 5 is believed to have been rendered moot. Applicants respectfully submit that claims 1-4, 6-

14, and 36-38 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

IV. Responses to the Rejections under 35 U.S.C. § 103(a)

Claims 1-3, 5-9, and 36-38 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over McMahan or the PRO-Q™ Product Information in view of Neville *et al.* (6 *Prot Sci* 2436-2445, 1997; hereinafter "Neville") and Nieba *et al.* (252 *Anal Biochem* 217-228, 1997; hereinafter "Nieba"). Claims 1, 2, and 4-14 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami *et al.* or the Ehteshami Dissertation in view of Neville and Nieba.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

IV.A. Response to the Obviousness Rejections over McMahan *or the PRO-Q™ Product Information in view of* Neville *and* Nieba

Claims 1-3, 5-9, and 36-38 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over McMahan or the PRO-Q™ Product Information in view of Neville and Nieba. According to the Patent Office, McMahan discloses a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-ion moiety, wherein the chelate is NTA, the metal is Ni^{2+}, and the detectable moiety is biotin. The PRO-Q™ Product Information is asserted to teach the same basic conjugate, and further a kit comprising the conjugate.

The Patent Office concedes that these references do not disclose that the metal ion is either Ga^{3+} or Fe^{3+}. The Patent Office asserts, however, that this deficiency is cured by the combination of Nieba and Neville. Nieba is asserted to teach that while Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are typically chelated to NTA, the choice of metal ion for IMAC should be optimized for highest selectivity relative to other proteins not carrying a His tag. Neville is asserted to teach that a Fe^{3+}-loaded NTA metal-ion affinity resin preferentially binds to phosphopeptides as compared to His-containing peptides. The Patent Office thus contends that it would have been obvious to one of ordinary skill in the

art to substitute a metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville in view of Nieba to achieve a metal chelate that recognizes phosphoproteins.

It appears that the Patent Office is interpreting Nieba to suggest that the disclosure related to metal ion optimization relates broadly to metal ions other than Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} and to applications other than binding to a His tag. Applicants respectfully submit that there is no support in the Nieba reference for such a broad interpretation. Rather, applicants respectfully submit that Nieba relates only to the optimization of binding conditions between the Ni^{2+}-NTA and a His tag. For example, every protein for which binding was desired in Nieba contained a His tag, and every conjugate tested was an Ni^{2+}-NTA conjugate. Applicants respectfully submit that there is no disclosure in Nieba that other metals can be used positively to selectively bind any protein that does not have a His tag.

Accordingly, applicants respectfully submit that when read in its entirety and in context, Nieba teaches no more than a general approach to maximizing the binding of an Ni^{2+}-NTA conjugate to His-tagged proteins while minimizing the binding of non-tagged proteins to the same Ni^{2+}-NTA conjugate. There is no suggestion in Nieba that any other metal can be employed for specifically detecting a protein that does not comprise a His tag, and as such, cannot be read to motivate the skilled artisan to attempt to optimize conditions for binding any chelate to a phosphoprotein.

Accordingly, applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine Nieba with Neville. Therefore, applicants respectfully submit that one of ordinary skill in the art would not, at the time the instant application was filed, have been motivated combine Neville in view of Nieba with McMahan or the PRO-Q™ Product Information to produce the phosphoprotein detection reagent (PPDR) comprising a detectable moiety of claim 1.

Thus, applicants respectfully submit that claim 1 has been distinguished over the combination of McMahan or the PRO-Q™ Product Information and Neville in view of Nieba. Claims 2, 3, 5-9, and 36-38 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. Claim 5 has been canceled, and thus the instant rejection is believed to be moot as to this claim. Therefore, applicants respectfully request that the instant rejection of claims 1-3, 6-9, and

36-38 be withdrawn. Applicants further respectfully submit that claims 1-3, 6-9, and 36-38 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

IV.B. Response to the Obviousness Rejections over Ehteshami et al. *or the* Ehteshami Dissertation *in view of* Neville *and* Nieba

Claims 1, 2, and 4-14 have been rejected under 35 U.S.C. § 103(a) upon the contentions that the claims are unpatentable over Ehteshami *et al.* or the Ehteshami Dissertation in view of Neville and Nieba. According to the Patent Office, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute a metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville in view of Nieba to produce a metal chelate that recognizes other proteins such as phosphoproteins. The Patent Office further asserts that one of ordinary skill in the art would have been motivated to modify the references because Nieba teaches that the choice of metal ion for IMAC can be optimized for the highest selectivity relative to other proteins not carrying a His tag.

Applicants respectfully submit that the remarks presented hereinabove are equally applicable to the instant rejection. Particularly, applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine Neville and Nieba because the Patent Office's assertions with respect to the disclosure of Nieba are based on an impermissibly broad reading of Nieba as discussed hereinabove. Thus, applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine Ehteshami *et al.* or the Ehteshami Dissertation with Neville and Nieba.

Furthermore, applicants respectfully submit that the various moieties found in the affinity reagents disclosed in Ehteshami *et al.* and the Ehteshami Dissertation have different functions than they do in the instantly claimed subject matter, and as such, if these affinity reagents were modified to contain Ga^{3+} or Fe^{3+}, would not function as phosphoprotein detection reagents.

For example, applicants respectfully submit that Ehteshami *et al.* and the Ehteshami Dissertation appear to disclose heterobifunctional polyethylene glycols. Particularly, both Ehteshami *et al.* and the Ehteshami Dissertation appear to disclose

biotin-PEG-iminodiacetic acid-copper conjugates for purifying avidin. As shown in Figure 1 of Ehteshami *et al.* and Figure 1.2 of the Ehteshami Dissertation, a chelating matrix coordinating a metal ion is bound to a solid support. The metal ion is also coordinated by a PEG derivative comprising a biotin moiety, or in the Ehteshami Dissertation, a "bioligand". This biotin/bioligand moiety functions in the disclosed PEG derivatives as the ligand that binds to the protein of interest, while the coordinated metal ion links the PEG derivative to the chelating matrix attached to the solid support. Thus, in the heterobifunctional polyethylene glycols disclosed in Ehteshami *et al.* and the Ehteshami Dissertation, the chelator-metal ion moiety binds to the PEG derivative.

This is in stark contrast to the function of the chelator-metal ion moiety present in the phosphoprotein detection reagent (PPDR) of claim 1. Applicants respectfully submit that section (ii) of claim 1 and section (d) of claim 10 clearly recite that the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein. As a result, even if one of ordinary skill in the art were motivated to replace the copper ion in the heterobifunctional polyethylene glycols disclosed in Ehteshami *et al.* and the Ehteshami Dissertation with Ga^{3+} or Fe^{3+}, the resulting chelator-metal ion moieties would still bind to the PEG derivative. In Ehteshami *et al.* and the Ehteshami Dissertation, it is the biotin/bioligand moiety that binds to the ligand of interest, and as such, applicants respectfully submit that the affinity reagents disclosed therein are functionally different than the PPDRs of claims 1 and 10.

Accordingly, applicants respectfully submit that claims 1 and 10 have been distinguished over the combination of combine Ehteshami *et al.* or the Ehteshami Dissertation and Neville in view of Nieba. Claims 2, 4-9, and 11-14 all depend directly or indirectly from claim 1 or claim 10, and thus are also believed to be distinguished over the cited combination. Claim 5 has been canceled, and thus the instant rejection is believed to be moot as to this claim. Therefore, applicants respectfully request that the instant rejection of claims 1, 2, 4, and 6-14 be withdrawn. Applicants further respectfully submit that claims 1, 2, 4, and 6-14 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In accordance with the amendments to the claims and the remarks presented hereinabove, applicants respectfully submit that claims 1-4, 6-14, and 36-38 are now in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

Should there be any minor issues outstanding in this matter, Examiner Fetterolf is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

Deposit Account

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

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